Organo Cascade Reactions | Hot Paper

DOI: 10.1002/ange.201405200

Asymmetric Synthesis of Highly Substituted β-Lactones through Oxidative Carbene Catalysis with LiCl as Cooperative Lewis Acid**

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Abstract: *The reaction of enals with β-diketones, β-ketoesters, and malonates bearing a β-oxyalkyl substituent at the α-position by oxidative NHC catalysis to provide highly substituted β-lactones is described. Reactions occur with excellent diastereo- and enantioselectivity. The organo cascade comprises two C–C bond formations and one C–O bond formation. Up to four contiguous stereogenic centers including two fully substituted stereocenters are formed in the cascade.*

Biologically active compounds can exert their activity through covalent bond formation with the targeted enzyme. Such covalent inhibitors contain carefully tuned reactive sites, which should show little unspecific reactivity with non-target enzymes. Interesting candidates along these lines are β-lactones.[1] Indeed, this structural motif can be found in many natural products with medicinal applications. As examples, the pancreatic lipase inhibitors lipstatin,[2] vibralactone,[3] and the proteasome inhibitor salinosporamide[4] containing a β-lactone moiety are depicted in Figure 1.

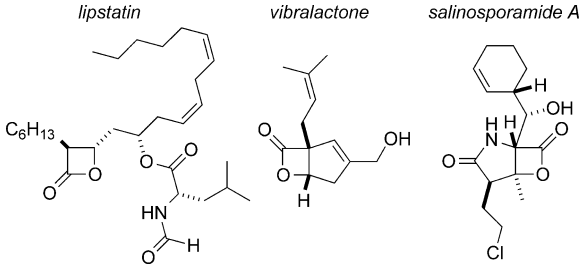
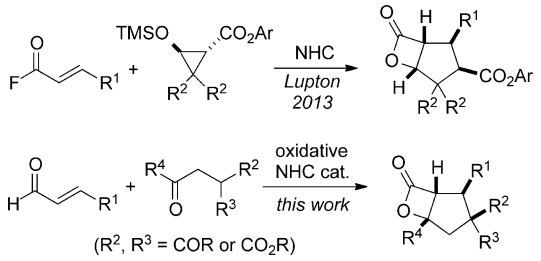


Figure 1. Biologically active β-lactones.

Organocatalysis has gained great attention over the past decade and various elegant processes have been reported to build up complex structures with high stereoselectivity in cascade reactions.[5] Structurally diverse compounds are accessible with readily available starting materials. Among others, N-heterocyclic carbenes (NHCs) have emerged as highly valuable catalysts for build-up of complex carbocyclic backbones.[6]

The preparation of β-lactones through NHC catalysis has been reported.[7,8] In these reactions, the Breslow intermediate derived from an enal and a NHC reacts as a nucleophile with an α,β-unsaturated ketone either intra-[7] or intermolecularly[8] in cascade processes to give the corresponding cyclopentane-anellated β-lactones. Depending on the substituents, the β-lactone moiety is not stable and CO_2-fragmentation eventually leads to highly substituted cyclopentenes.[7a,c,8a,b]

α,β-Unsaturated acylazolium ions either generated from the Breslow-intermediate under oxidative conditions[9] or by reaction of an acyl fluoride with a NHC[10,11] are relatively weak electrophiles.[12] Recently, Lupton and co-workers reported an elegant organo cascade proceeding via α,β-unsaturated acylazolium ions using donor–acceptor cyclopropanes as pronucleophiles for the stereoselective synthesis of highly substituted β-lactones (Scheme 1).[13] We disclose



Scheme 1. β-Lactone synthesis via α,β-unsaturated acylazolium ions.

herein intermolecular reactions of enals with β-diketones, β-ketoesters, and malonates bearing a β-oxyalkyl substituent at the α-position by oxidative NHC catalysis. As compared to the complementary Lupton approach, the starting materials are more readily prepared and β-lactones with a different substitution pattern are accessible. Highly substituted cyclopentanes containing up to four consecutive stereogenic centers including two fully substituted stereocenters are obtained. Notable, these are the first examples on the efficient conjugate additions of tertiary prochiral C-nucleophiles to α,β-unsaturated acylazolium ions. Similar transformations can be achieved with α,β-unsaturated acylammonium ions as acceptors, as Romo and co-workers reported very recently.[14]

We started our investigations using cinnamaldehyde **1a** and malonate **2a** as substrates. As oxidant, bisquinone **3**[15] (1.2 equiv) was chosen and optimizations were conducted using the chiral salts **A**[16] or **B**[17] (5 mol%) as NHC

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[**] This work was financially supported by the NRW Graduate School of Chemistry and the SFB 858.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201405200.

precursors. We were pleased to find that with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.2 equiv) as a base and **A** as the catalyst, the reaction proceeded efficiently at room temperature in THF to give lactone **4aa** within 2 h in 84% yield with complete diastereoselectivity and 48% enantiomeric excess (Table 1, entry 1). The assignment of the relative configuration of **4aa** is based on X-ray analysis[18] and the absolute configuration was assigned by comparison of the optical rotation with a known literature value.[14] Similar results were achieved in toluene and acetonitrile as solvents (entries 2 and 3). The diastereoselectivity was also excellent using precatalyst **B** and yields of more than 90% were obtained. In toluene, the *ee* was 55%; however, it significantly dropped upon changing the solvent to CH_3CN (entries 4 and 5).

To improve the enantioselectivity, we decided to add LiCl as a cooperative Lewis acid.[19] In THF with catalyst **B** and 2 equiv of LiCl, the enantioselectivity increased to 63% (entry 6). In toluene the Li-salt had an accelerating effect on the organo cascade but the *ee* decreased (entry 7). However, using toluene and catalyst **A** led to a significant increase of the *ee* upon the addition of LiCl and **4aa** was isolated in good yield and selectivity (88% *ee*, entry 8). Lowering the reaction temperature to 0°C provided nearly the same selectivity (entry 9). In THF in the presence of LiCl only little conversion was achieved (entry 10). Other bases, such as Cs_2CO_3, KO*t*Bu, or K_3PO_4 afforded only traces of the targeted lactone (entries 11–13). A high selectivity was also observed for Et_2NiPr as base; however, the reactivity was low in that case and the reaction time had to be increased (entry 14).

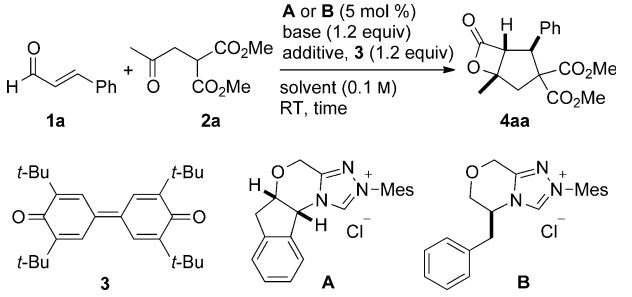
We further tested whether the amount of Li-salt has any effect on the selectivity and found a slightly higher *ee* with 1.5 equiv LiCl (entries 8, 15, and 16). At this Li-salt concentration in DCE, the selectivity was good but the reaction was slower (entry 17) and trifluorotoluene turned out to be not a suitable solvent for this cascade reaction (entry 18). The best result was obtained in dichloromethane using catalyst **A** with 0.5 equiv of LiCl and **4aa** was isolated in an almost quantitative yield with 95% *ee* (entry 19). Upon increasing the Li-salt concentration to 1 equiv we found that product decomposition occurred in DCM and decreasing the LiCl loading from 0.5 to 0.2 equivalents did not change the reaction outcome (entry 20). However, for convenience we decided to use 0.5 equiv of LiCl in all follow-up experiments.

Under optimized conditions (Table 1, entry 19), the scope and limitations of the novel cascade reaction were studied. Along with cinnamaldehyde, we used *p*-methoxy cinnamaldehyde **1b** ($R^1 = OMe$) and the *p*-nitro congener **1c** ($R^1 = NO_2$). For all reactions investigated in this series, the diastereoselectivity was excellent (d.r. > 99:1). Using malonate **1a** as nucleophile, the cascade reactions proceeded with a high enantioselectivity and the lactones **4ba** and **4ca** were isolated in 94% *ee* and 96% *ee*, respectively (Table 2, entries 1 and 2). Compared to cinnamaldehyde **1a** and its *p*-methoxy derivative **1c**, the reaction of the electron-poorer *p*-nitro derivative **1b** gave a lower yield in the series. Looking at the effect of the ester substituent at the malonate moiety, we found the allyl malonate **2b** ($R^2 = Me$, $R^3 = OAllyl$) and benzyl malonate **2c** ($R^2 = Me$, $R^3 = OBn$) to be more reactive than the methyl congener **2a**. Reactions with enals **1a–c** were faster and the selectivities were very good in all cases (entries 3–8).

We were pleased to find that the organo cascade also works highly efficient with the β-diketone **2d** as nucleophile ($R^2 = R^3 = Me$). For all three aldehydes tested, the corresponding β-lactones **4ad**, **4bd**, and **4cd** were isolated in good yield with excellent *ee* (> 99% *ee*, entries 9–11). The absolute configuration of **4ad** was unambiguously assigned by X-ray analysis.[18] The R^2-substituent was varied next and we noted that ethyl and the isopropyl group are tolerated at that site (entries 12 and 13). The corresponding β-lactones **4ae** and **4af** were isolated with high enantioselectivity in good to excellent yield. With the bulky *tert*-butylketone, the reaction was very sluggish and only 15% yield was achieved after 72 h reaction time (see **4ag**, entry 14).

When the R^2-substituent is a phenyl group as in **2h–j**, a different reaction outcome was observed. The organo cascade of **2h** with **1a** provided cyclopentene **5a** in quantitative yield and 91% *ee* (Scheme 2). A similar result was obtained with allyl malonate **2i** to give **5b**; however, the

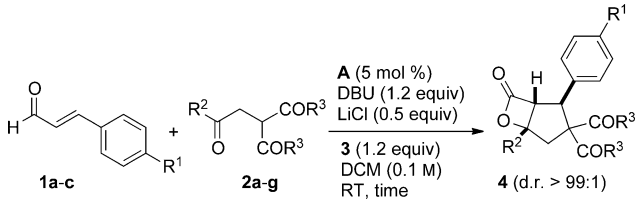
Table 1: Reaction optimization.



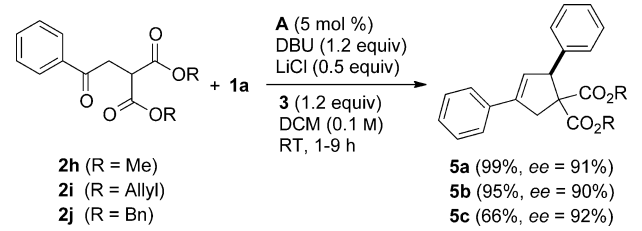
Entry	LiCl [equiv]	Base	Cat.	Solvent	Time [h]	Yield [%][a]	*ee* [%][b]
1	–	DBU	**A**	THF	2	84	48
2	–	DBU	**A**	PhMe	2	88	50
3	–	DBU	**A**[c]	CH_3CN	3	75	53
4	–	DBU	**B**	PhMe	3	91	55[d]
5	–	DBU	**B**[c]	CH_3CN	0.5	97	10[d]
6	2	DBU	**B**	THF	1.5	75	63[d]
7	1	DBU	**B**[c]	PhMe	0.75	88	50[d]
8	1	DBU	**A**	PhMe	1	88	88
9[e]	1	DBU	**A**	PhMe	4	70	86
10	1	DBU	**A**[c]	THF	12	< 5	n.d.
11	1	Cs_2CO_3	**A**	PhMe	12	< 5	n.d.
12	1	KO*t*Bu	**A**	PhMe	24	< 5	n.d.
13	1	K_3PO_4	**A**	PhMe	24	< 5	n.d.
14	2	Et_2NiPr	**A**	PhMe	22	75	92
15	0.5	DBU	**A**	PhMe	1	88	82
16	1.5	DBU	**A**[c]	PhMe	0.75	80	91
17	1.5	DBU	**A**	DCE	2.5	88	87
18	1.0	DBU	**A**	$PhCF_3$	24	< 5	n.d.
19	**0.5**	**DBU**	**A**	**DCM**	**2**	**98**	**95**
20	0.2	DBU	**A**	DCM	2	98	95

[a] Yield of the isolated product. [b] Determined by HPLC (see the Supporting Information). [c] 2.5 mol% catalyst was used. [d] The other enantiomer was formed. [e] Conducted at 0°C. n.d. = not determined.

Table 2: Preparation of various β-lactones: variation of the enal and the C-nucleophile.



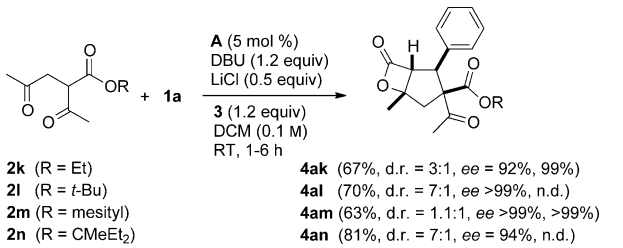
Entry	Substrate **1** (R^1)	Substrate **2** (R^2, R^3)	Time [h]	Product	Yield [%]	*ee* [%]
1	**1b** (NO_2)	**2a** (Me, OMe)	4.5	**4ba**	45	94
2	**1c** (OMe)	**2a** (Me, OMe)	5	**4ca**	90	96
3	**1a** (H)	**2b** (Me, OAllyl)	2	**4ab**	95	95
4	**1b** (NO_2)	**2b** (Me, OAllyl)	2	**4bb**	75	93
5	**1c** (OMe)	**2b** (Me, OAllyl)	2.5	**4cb**	80	>99
6	**1a** (H)	**2c** (Me, OBn)	1	**4ac**	87	>99
7	**1b** (NO_2)	**2c** (Me, OBn)	3	**4bc**	60	94
8	**1c** (OMe)	**2c** (Me, OBn)	3	**4cc**	94	97
9	**1a** (H)	**2d** (Me, Me)	3	**4ad**	95	>99
10	**1b** (NO_2)	**2d** (Me, Me)	2.5	**4bd**	85	>99
11	**1c** (OMe)	**2d** (Me, Me)	3.5	**4cd**	80	>99
12	**1a** (H)	**2e** (Et, OBn)	1	**4ae**	97	94
13	**1a** (H)	**2f** (*i*Pr, OBn)	24	**4af**	73	94
14	**1a** (H)	**2g** (*t*Bu, OMe)	72	**4ag**	15	n.d.



Scheme 2. Preparation of cyclopentenes.

benzyl malonate **2j** produced cyclopentene **5c** in a lower yield with a similar *ee*. It is apparent that these cyclopentenes derive from the corresponding β-lactones through CO_2 expulsion.[7a,c,8a,b,20]

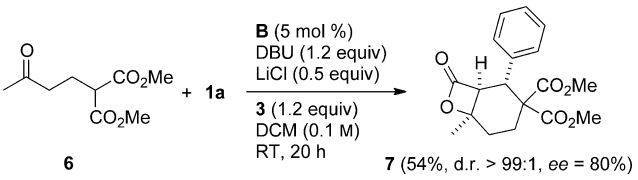
We then studied whether our method allows controlling the build-up of two fully substituted stereogenic centers. To this end, diketones **2k-n** were prepared and reacted under optimized conditions with **1a** (Scheme 3). The ethyl ester **2k** underwent the reaction smoothly and the lactone **4ak** was obtained as a 3:1 mixture of separable diastereoisomers in 67% combined yield. The absolute configuration of the major



Scheme 3. β-Lactones with two fully substituted stereogenic centers.

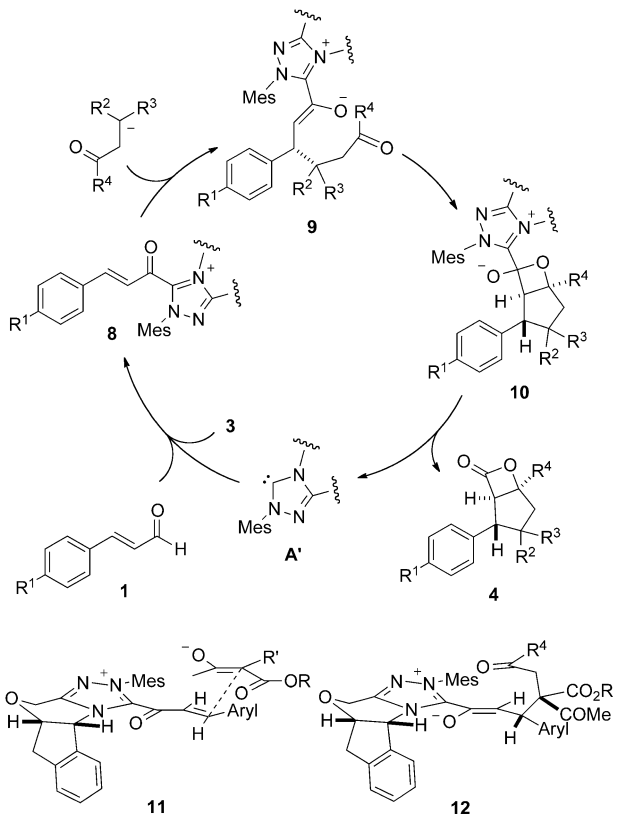
isomer, which was obtained with 92% *ee*, was assigned by X-ray analysis.[18] The minor diastereoisomer was formed with 99% *ee*. Pleasingly, the diastereoselectivity increased upon switching to the *tert*-butyl ester **2l** (d.r. = 7:1) and the major isomer was formed with excellent *ee* (>99%). With the bulky mesityl ester **2m**, the addition of the prochiral C-nucleophile occurred with excellent *ee*. However, the diastereoselectivity was low (see **4am**). Encouraged by the *tert*-butyl system, we further increased the steric bulk at the ester moiety and investigated the β-ketoester **2n**. Unfortunately, the diastereoselectivity could not be further increased (see **4an**) and in comparison to the *tert*-butyl ester, the *ee* was slightly decreased (94%).

Finally, we tested whether the organo cascade can also be used for the preparation of cyclohexane-anellated β-lactones and malonate **6** was reacted with cinnamaldehyde under oxidative NHC catalysis in the presence of LiCl. Disappointingly, the reaction did not work with catalyst **A** under standard conditions. We therefore switched to catalyst **B** and observed that the cascade proceeded slowly and **7** was isolated in 54% yield with complete diastereoselectivity and 80% *ee* (Scheme 4). The relative configuration was unambiguously assigned by X-ray analysis.[18,21]



Scheme 4. Preparation of cyclohexane-anellated β-lactone **7**.

We propose the following mechanism for the organo cascade leading to β-lactones of type **4** (Scheme 5). The reaction to the homologue **7** works analogously. First, the NHC **A′**, generated by deprotonation of salt **A**, reacts with the enal **1** to give the corresponding Breslow intermediate which is oxidized by **3** to the acylazolium ion **8**. A Michael addition of deprotonated **2** to **8** gives the enolate **9**, which undergoes a concerted, asynchronous formal [2+2] aldol lactonization process to give intermediate **10**, as recently suggested.[7d] Fragmentation of **10** to **A′** eventually leads to product **4**. Alternatively, **9** can react in a two-step sequence through an intramolecular aldol reaction and subsequent intramolecular addition of the alkoxide to the intermediate acylazolium ion to give **10**. The enantioselectivity can be understood when considering the structure of the acylazolium ion, in which one face of the Michael acceptor is well-shielded by the NHC substituents (see **11**). We assume the deprotonated ketoester to react as depicted in **11**, leading to **12**, in which the bulky ester is close to the β-H-atom of the Michael acceptor, thereby steering the diastereoselectivity in the addition step. This explains why the highest selectivity is obtained for the bulkier esters. A similar organization of the transition state was found for the addition of deprotonated acetylacetone to an acylazolium ion by calculations.[12a] Currently, we do not fully understand the role of the Li-salt



Scheme 5. Proposed mechanism.

for the selectivity. The higher reactivity in the presence of the Li-salt is likely caused by Li-complexation of the O-atom of the acylazolium ion which should lower the LUMO and hence activate the Michael acceptor.

In summary, we reported an organo cascade of enals with β-diketones, β-ketoesters, or malonates comprising a Michael addition followed by a formal [2+2] aldol lactonization to give highly substituted β-lactones. Notably, β-lactones are biologically interesting compounds. The novel organo cascade uses a chiral NHC as a catalyst and proceeds under mild conditions using a readily available bisquinone oxidant. In the process, four contiguous stereogenic centers can be generated. Importantly, we showed that with LiCl as cooperative Lewis acid, the cascade reaction proceeds with excellent diastereo- and enantioselectivity. The reactions are experimentally easy to accomplish by simply mixing catalyst, reagents, and substrates at room temperature.

Received: May 12, 2014
Published online: July 11, 2014

Keywords: asymmetric synthesis · cooperative catalysis · β-lactones · N-heterocyclic carbenes · organo catalysis

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[21] The lactone **7** slowly decomposed to the corresponding cyclohexene derivative through CO_2 fragmentation.